REVIEW

Diagnostic approach to patients with suspected vasculitis

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Vasculitis presents several diagnostic challenges. Firstly, patients could present with protean clinical manifestations with a wide spectrum ranging from isolated cutaneous vasculitis to multisystem involvement. Secondly, there are several medical conditions that could mimic the presentation of vasculitis. The range of differential diagnosis is therefore broad. Thirdly, vasculitis could occur as a primary disorder or be secondary to various medical conditions. It becomes important to differentiate them, as treatment of some forms of vasculitis such as those that are secondary to infection or drugs, is different from that of primary vasculitis. Fourthly, there are several different forms of vasculitis. Some are benign and self limiting, while others have the potential to threaten vital organ function and life. It follows that a rational approach is required during evaluation of patients with suspected vasculitis.

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Vasculitis means inflammation of the blood vessel wall. Any type of blood vessel in any organ could be affected.

Clinical manifestations arise because:

- Systemic inflammatory response resulting from release of chemical mediators from inflamed blood vessels gives rise to various non-specific systemic manifestations. They include fever, night sweats, malaise, weight loss, arthralgia, myalgia and laboratory features such as normocytic and normochromic anaemia, leucocytosis, thrombocytosis, and raised erthyrocyte sedimentation rate (ESR) and C reactive protein (CRP). Some patients, especially early in the course of their illness, could present with isolated systemic manifestations posing a diagnostic challenge. Conversely, systemic inflammatory response is not seen in most patients with localised forms of vasculitis.
- More specific manifestations from involvement of various organ systems arise from one or both of the following mechanisms[1]:

(1) Thinning of vessel wall due to inflammatory cell infiltration: This leads to increased vascular permeability or vessel wall rupture. Haemorrhage occurs into the affected organ. Clinical presentation depends on site of involvement. If only cutaneous venules are involved, red cell transudation or haemorrhage occurs within skin presenting with palpable purpura. If pulmonary capillaries are involved, presentation could be more dramatic with haemorrhage occurring into alveoli presenting with breathlessness and haemoptysis.

(2) Narrowing or complete occlusion of affected vessel because of vascular intimal proliferation and intraluminal thrombus formation: This leads to ischaemia or infarction of affected organs. Examples of presenting manifestations are necrotic skin ulcers, mononeuritis multiplex, or infarction of a major organ depending on site of involvement.

Thus, vasculitis should be suspected in patients with unexplained ischaemia (that which occurs in the absence of risk factors for atherosclerotic vascular disease) or multisystem disease especially in the presence of systemic inflammatory response or features such as palpable purpura, mononeuritis multiplex, or glomerulonephritis.[1] Depending on type of blood vessel affected and extent of involvement, clinical presentation could range from isolated benign and self limiting cutaneous vasculitis to life threatening widespread internal organ involvement.[2–6]

Table 1 outlines the clinical features of vasculitis on the basis of size of affected vessels. It should however be noted that most forms of vasculitis actually do not respect vessel size boundaries, and considerable overlap occurs. I have used this classification only as it helps to understand clinical presentations better.

GENERAL DIAGNOSTIC APPROACH

There are five important questions to ask when faced with a patient with possible vasculitis (depending on clinical presentation):

(1) Is this a condition that could mimic the presentation of vasculitis?
(2) Is there a secondary underlying cause?
(3) What is the extent of vasculitis?
(4) How do I confirm the diagnosis of vasculitis?
(5) What specific type of vasculitis is this?

Vasculitis ''mimics'' should be excluded first

Several conditions could mimic vasculitis[7–9] and need to be considered in the differential diagnosis depending on clinical presentation.

Firstly, infection is a great mimic of vasculitis (see box 1). Several clinical and laboratory features are common to both vasculitis and infection. Constitutional symptoms such as

Abbreviations: ESR, erthyrocyte sedimentation rate; CRP, C reactive protein; ANCA, antineutrophil cytoplasmic antibody; p-ANCA, perinuclear ANCA; ELISA, enzyme linked immunosorbent assay; AAV, ANCA associated vasculitides; IF, immunofluorescence

Table 1 Clinical features of vasculitis on the basis of size of the affected blood vessel

Size of blood vessel	Blood vessel involved	Clinical features
Small vessel vasculitis (vessels smaller than arteries such as capillaries and venules)	Cutaneous post-capillary venules	Palpable purpura
	Glomerular capillaries	Haematuria, red cell casts in urine, proteinuria, and decline in renal function
	Pulmonary capillaries	Lung haemorrhage manifesting as breathlessness, haemoptysis and widespread alveolar shadowing on chest radiograph
Medium vessel vasculitis (small and medium sized arteries)	Small cutaneous arteries	Necrotic lesions and ulcers, nail fold infarcts
	Epineural arteries	Mononeuritis multiplex
	Mesenteric artery	Abdominal pain, gastrointestinal bleeding and perforation because of gut infarction
	Branches of coeliac artery	Infarction of liver, spleen, or pancreas
	Renal artery	Renal infarction
	Coronary arteries	Myocardial infarction or angina, coronary artery aneurysm, ischaemic cardiomyopathy
	Small pulmonary arteries	Necrotic lesions leading to cavitating lung shadows on chest radiograph
	Small arteries in ear, nose and throat region	Nasal crusting, epistaxis, sinusitis, deafness, stridor because of sub-glottic stenosis
Large vessel vasculitis (aorta and its branches)	Extracranial branches of carotid artery	Temporal headache (temporal artery), blindness (ophthalmic artery), jaw claudication (vessels supplying muscles of mastication)
	Thoracic aorta and its branches	Limb claudication, absent pulses and unequal blood pressure, bruits, thoracic aortic aneurysms

fever, malaise, arthralgia, myalgia and weight loss, and laboratory features such as normocytic normochromic anaemia, peripheral blood leucocytosis, thrombocytosis, raised ESR, and CRP are encountered in both. Because treatment of vasculitis entails the use of immunosuppressive drugs, the consequences of not recognising infection would be disastrous. Thus, it is mandatory to perform a full and appropriate infection screen in all patients with suspected vasculitis especially those who present with systemic inflammatory features. It has been suggested that procalcitonin levels are raised in patients with infection but not in those with non-infective inflammatory conditions,[10] but this test is not widely available.

Apart from infection, several rare conditions including thrombotic disorders such as antiphospholipid antibody syndrome,[11] thrombotic thrombocytopenic purpura,[12] and sickle cell disease, embolisation from atrial myxoma[13 14] and cholesterol emboli from atheroma,[15] non-inflammatory vessel wall disorders such as fibromuscular dysplasia,[16] amyloidosis[17] and scurvy,[18] and vasospasm due to ergot[19] could all mimic presentation of vasculitis by causing ischaemic manifestations or systemic symptoms.[20] If vasculitis were confined to one or few organ systems, differential diagnosis becomes even broader. Thus, for example, radiological finding of multiple nodular lung shadowing could occur with not only Wegener's granulomatosis but also with a wide variety of other conditions including lung metastases and infection.

Box 1 Illustrative case 1

A 48 year old man, an injecting drug user, presented with a four week history of generally feeling unwell and purpuric rash over both legs. He looked ill, and there were several nail fold infarcts and vasculitic lesions over the pulps of his fingers. Blood picture was in keeping with systemic inflammatory response. Chest radiography showed two separate cavitating lesions in the right lung. Skin biopsy showed leucocytoclastic vasculitis. His illness was initially attributed to systemic vasculitis and specialist opinion was sought.

Several days after admission, on the advice of the respiratory physicians, serial blood cultures and echocardiogram were arranged and the patient was presumptively given broad spectrum antibiotics. Blood cultures grew *Staphylococcus aereus* and transthoracic echocardiogram showed vegetations around the tricuspid valve consistent with right heart endocarditis. The cavitating lesions were most probably lung abscesses secondary to septic emboli.

Possible secondary causes of vasculitis should be excluded

Because treatment of some forms of vasculitis such as those that are secondary to infection or drugs is different from that of primary vasculitis, it is important to exclude such conditions that are likely to cause secondary vasculitis (box 2).

Infections often coexist with vasculitis, and some infections such as hepatitis B and C, human immunodeficiency virus, infective endocarditis, and tuberculosis are an important secondary cause of vasculitis.[21–25] Presence of coexistent infection or an underlying infectious aetiology would change management of vasculitis. Immunosuppressive therapy that is used to treat patients with primary vasculitis could lead to disastrous consequences in the face of unrecognised infection. Thus, for example, patients with infected vasculitic leg ulcer should first receive appropriate antibiotic treatment to eradicate the infection before starting treatment for vasculitis, and those with polyarteritis nodosa secondary to hepatitis B infection should be treated with antiviral drugs and not cyclophosphamide.[26]

Most forms of secondary vasculitis are extremely rare with the possible exception of rheumatoid vasculitis.[20] Vasculitis is seldom the initial presenting manifestation when it occurs in the setting of rheumatoid arthritis or systemic lupus erythematosus, and is thus readily diagnosed by features of the parent illness. Among the secondary causes, drug induced

vasculitis deserves special mention as resolution of vasculitis is likely to occur after withdrawal of the offending agent.[27] Patients could present with a wide range of manifestations ranging from isolated cutaneous vasculitis to widespread internal organ involvement. Drugs such as hydralazine, propylthiouracil, and montelukast have been implicated in the causation of ANCA (antineutrophil cytoplasmic antibody) associated vasculitis. The ANCA is usually targeted against myeoperoxidase (perinuclear ANCA (p-ANCA))[28] (see below). Clinical presentation might be indistinguishable from idiopathic ANCA associated systemic vasculitides such as Wegener's granulomatosis or Churg-Strauss syndrome.[29] A comprehensive drug history should therefore be obtained from all patients presenting with vasculitic manifestations.

Extent of vasculitis should be assessed

It is important to assess the extent of vasculitis, and look for internal organ involvement even in patients who seem to have isolated cutaneous vasculitis. Both cutaneous leucocytoclastic angiitis and microscopic polyangiitis (see below) can present with palpable purpura, but while the first is usually a self limiting form of vasculitis that is often restricted to the skin, the second can be complicated by life threatening internal organ involvement.[31]

Extensive involvement and threat to vital organ function call for aggressive management. For example, combination therapy with cyclophosphamide and methylprednisolone is offered to those with renal involvement in Wegener's granulomatosis to prevent progression to end stage renal disease,[32] while even co-trimoxazole is sufficient treatment for some patients with disease limited to the upper respiratory tract[33] (see box 3). Another example is giant cell arteritis. Patients with temporal headache and no visual symptoms usually need about 40 milligrams of prednisolone/day,[34] but a much higher dose needs to be started promptly for those with imminent threat to sight.[35]

A thorough history and detailed physical examination supplemented with a few simple investigations such as urine dipstick and chest radiography should be sufficient in most patients to assess extent of involvement with vasculitis.

Histological and/or radiological proof of vasculitis should be obtained

Clinical evaluation should be focused towards identifying a suitable site for biopsy, as tissue diagnosis is vital to confirming the diagnosis of vasculitis. The site to be biopsied depends on clinical presentation. Common favoured sites include skin, kidney, temporal artery, muscle, nasal mucosa, lung, sural nerve, and testis. If clinical evidence of multisystem involvement were present, choice of biopsy site would depend on its likelihood of affecting treatment decisions. In patients with skin and renal involvement, renal biopsy is preferred, as detection of necrotising glomerulonephritis not only helps to confirm the diagnosis of vasculitis but also to decide how aggressive treatment should be. Blind biopsies to "exclude vasculitis" in patients with non-specific generalised systemic symptoms are usually unhelpful.

Biopsy findings might sometimes not be helpful even in patients with definite vasculitis. Histological examination could be normal (yield with sural nerve biopsies in patients with definite vasculitis is only around 45%[36]) or show only non-specific findings. For example, necrotising granulomas are not always seen in nasal mucosal or lung biopsy specimens from patients with suspected Wegener's granulomatosis.[37 38] Hence, presence of even non-specific inflammation in the absence of infection or malignancy associated with positive c-ANCA and anti-PR3 (see below) in the right clinical context should be sufficient to diagnose Wegener's granulomatosis.

Although it would be prudent to wait for biopsy results to be available before starting specific treatment, with some forms of vasculitis such as giant cell arteritis (elderly patients with new onset headache and raised ESR), treatment with corticosteroids should be started, even before organising a temporal artery biopsy, to prevent risk of blindness.[39] There are some patients in whom biopsy confirmation is not essential. For example, rheumatoid vasculitis is certain in a patient with rheumatoid arthritis who develops nail fold infarcts, palpable purpura, mononeuritis multiplex, and necrotic leg ulcers.

If tissue diagnosis is impractical (patients with large or medium vessel vasculitis with no accessible tissue for obtaining histological proof), angiogram should be considered. For example, mesenteric and coeliac axis angiograms are useful in patients with suspected gastrointestinal tract vasculitis, while renal angiogram is useful in those with suspected renal artery involvement (not glomerulonephritis, which is best diagnosed with renal biopsy). Recently, computed tomographic angiography has been used to permit rapid diagnosis in patients with suspected polyarteritis nodosa.[40] Characteristic angiographic findings in patients with medium vessel vasculitis (polyarteritis nodosa) include multiple microaneurysms (attributable to necrotising inflammation through vessel wall with consequent weakening).[41] Magnetic resonance angiogram of the thoracic aorta is the investigation of choice in patients with suspected large vessel vasculitis such as Takayasu's arteritis (see below).[42 43] This would show stenosis, occlusion, or aneurysm formation.

Box 2 Secondary causes of vasculitis (modified from Gross *et al*[30]

- Inflammatory diseases of unknown aetiology: rheumatoid vasculitis, vasculitis associated with systemic lupus erythematosus and Sjogren's syndrome, inflammatory bowel disease, sarcoidosis
- Infectious diseases: hepatitis B and C, human immunodeficiency virus, mycobacteria, syphilis
- Neoplasia: haematological malignancies such as myeloproliferative and lymphoproliferative disorders, solid tumours
- Drugs (almost any drug)

Box 3 Illustrative case 2

A 62 year old previously healthy woman presented to the otolaryngologist with nasal crusting, epistaxis, and recurrent sinusitis. Serum c-ANCA (cytoplasmic ANCA) was positive by indirect immunofluorescence with anti-PR3 (anti-proteinase 3) by enzyme linked immunosorbent assay (ELISA). Biopsy of her nasal mucosa showed features in keeping with necrotising vasculitis. A diagnosis of Wegener's granulomatosis was made, and she was referred to the rheumatologist.

Further evaluation showed multiple nodular shadows on chest radiography (she denied any respiratory symptoms), and blood and protein on urine dipstick testing. Urine microscopy showed red cell casts and renal biopsy showed necrotising glomerulonephritis. Remission was induced with methylprednisolone and cyclophosphamide combination treatment.

The specific type of vasculitis should be identified (where possible)

Finally, it would be useful to identify the type of vasculitis, as vasculitides with identical clinical presentation can have different prognoses. For example, Henoch-Schonlein purpura and microscopic polyangiitis can both present with palpable purpura and glomerulonephritis but prognosis is much better for patients with Henoch-Schonlein purpura[44 45] (see box 4).

The first step towards identifying the specific type of vasculitis is to categorise them according to the size of the affected vessel[46] (see box 5 and table 1). Patients in whom large vessel vasculitis[39] is suspected on the basis of involvement of aorta and its branches can then be labelled as either giant cell arteritis or Takayasu's arteritis depending on their age, ethnic origin, and preference for involvement of specific blood vessels. Giant cell arteritis[34] is probable in a white patient >50 years of age with preferential involvement of extracranial branches of the carotid artery, while Takayasu's arteritis is probable in a Far Eastern patient <50 years of age with preferential involvement of thoracic aorta and its branches supplying upper limbs.

Polyarteritis nodosa is the prototype of medium vessel vasculitis. By definition, patients with small vessel involvement such as glomerulonephritis or pulmonary capillaritis should not be labelled as polyarteritis nodosa.[47] Renal involvement can however still occur in polyarteritis nodosa because of hypertension or involvement of medium sized renal arteries leading to renal infarction. Kawasaki's disease[48] is the equivalent of polyarteritis nodosa that occurs in young children. It is characterised by preferential involvement of coronary arteries leading to formation of coronary artery aneurysm and myocardial infarction.

Small vessel vasculitides are broadly subclassified on the basis of whether pathogenesis involves antibody mediated cytotoxicity or immune complex formation. It is particularly important to recognise those patients in whom vasculitis is likely to be caused by antibody mediated cytotoxicity, as they are prone to developing glomerulonephritis and (rarely) pulmonary capillaritis that require prompt treatment with immunosuppressive drugs. Absence of immune deposits on biopsy and presence of ANCA in serum can help to identify such patients. ANCA associated vasculitides (AAV) not only affect small vessels but also medium sized vessels such as arteries.

Box 4 Illustrative case 3

A 56 year old man presented with three week history of generalised arthralgia, abdominal pain, and rash around both ankles. His medical history was unremarkable, and he was not taking regular medication. Physical examination showed palpable purpura around both ankles, but nothing else. Urine dipstick testing showed blood and protein. Skin biopsy showed leucocytoclastic vasculitis, but immunofluorescence was unfortunately not requested. Both p and c-ANCA were negative. A presumptive diagnosis of Henoch-Schonlein purpura was made, and his symptoms resolved within the next couple of weeks.

He re-presented a few months later with recurrence of rash and abdominal pain, and was referred to the rheumatologist. Urine dipstick testing still showed presence of blood and protein. There was now evidence of renal impairment. Renal biopsy showed pauci-immune necrotising glomerulonephritis with evidence of scarring as well. Despite treatment with pulsed corticosteroids and cyclophosphamide, renal function could not be improved.

Box 5 Classification of vasculitis on the basis of size of affected blood vessel

Large vessel vasculitis
- Giant cell arteritis
- Takayasu's arteritis

Medium vessel vasculitis
- Polyarteritis nodosa
- Kawasaki's disease

Small vessel vasculitis
- ANCA associated vasculitis
- (Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis)
- Henoch-Schonlein purpura
- Cutaneous leucocytoclastic angiitis
- Cryoglobulinaemic vasculitis

Box 6 Important investigations to consider during initial evaluation of patients with suspected vasculitis (depending on clinical presentation)

To exclude vasculitis ''mimics'' and secondary causes
- Blood cultures
- Echocardiogram
- Hepatitis screen (B and C)
- HIV test
- Antiglomerular basement membrane antibody
- Antiphospholipid antibodies
- Antinuclear antibody

To assess extent of vasculitis
- Urine dipstick and microscopy (all patients)
- Chest radiography (all patients)
- Nerve conduction studies/electromyography/CK

To confirm diagnosis of vasculitis
- Biopsy and/or angiogram

To identify the specific type of vasculitis
- ANCA
- Cryoglobulin
- Complement levels
- Eosinophil counts/IgE levels
- Specific findings on biopsy (necrotising granulomatous inflammation, presence of IgA deposits, evidence of immune complex formation (or its absence))

Two types of ANCA staining patterns are seen on immunofluorescence (IF), namely cytoplasmic (c-ANCA) and perinuclear (p-ANCA).[49] ELISA should then always be performed in patients with positive results on immunofluorescence (IF) to identify the specific antigen targeted by ANCA. Presence of c-ANCA with anti-proteinase 3 (anti-PR3) is highly suggestive of Wegener's granulomatosis, while p-ANCA with anti-myeloperoxidase (anti-MPO) is more often

encountered in those Churg-Strauss syndrome and microscopic polyangiitis.

Although the negative predictive value of IF for AAV was found to be around 97% in one cohort, the positive predictive value (PPV) of positive IF for AAV is only around 45%. PPV of both positive IF and positive ELISA combined together for AAV increases to around 88%. For a positive IF test alone, sensitivity for AAV is around 67% and specificity is around 93%. For combined IF and ELISA, sensitivity decreases to around 52%, but specificity increases to 99%.[50] Other groups have also shown similar figures and reinforced the value of confirming positive IF test results with ELISA.[51–53] It is worth mentioning here that false positive ANCA results could be seen in a wide variety of conditions especially when positive IF results are not confirmed by ELISA. Conversely, ANCA can be negative in a significant proportion of patients with AAV (10%–20% of active, untreated Wegener's granulomatosis, 30% of limited Wegener's granulomatosis, 30% of MPA, and 50% of Churg-Strauss syndrome patients in most series)[49] (see box 4). Thus, ANCA test should not be requested unless there is clinical suspicion of vasculitis,[53] and its absence should not be taken as evidence against AAV.

Presence of features such as late onset asthma, nasal polyps, and hypereosinophilia with necrotising granulomatous inflammation would favour Churg-Strauss syndrome, while necrotising granulomatous inflammation with preferential involvement of upper and lower respiratory tracts and kidneys would favour Wegener's granulomatosis. Absence of granulomatous inflammation would favour MPA. However, as choice of therapeutic regimen for AAV is dependent on extent of vasculitis, identification of the specific type of AAV is unimportant during initial evaluation.

Other forms of small vessel vasculitis (those that are immune complex mediated) could be identified by presence of other features. In a patient with joint pains, palpable purpura, abdominal pain, and nephritis, the presence of vascular IgA deposits on biopsy is diagnostic of Henoch-Schonlein purpura. Presence of cryoglobulin in serum is suggestive of cryoglobulinaemic vasculitis. Cutaneous leucocytoclastic angiitis, which has an excellent prognosis, is a diagnosis of exclusion. Because histological examination of cutaneous leucocytoclastic angiitis is similar to that of dermal lesions occurring as a component of systemic small vessel vasculitides, it is important to exclude systemic disease in such patients.[31]

CONCLUSION

In summary, patients in whom vasculitis is suspected need detailed medical evaluation (box 6). Because treatment of most primary forms of vasculitis consists of potentially toxic immunosuppressive therapy, exclusion of conditions that could mimic or cause vasculitis (especially infection and drug exposure) should take priority. Assessment of extent of disease, especially renal involvement, is equally important. Histological or radiological proof of vasculitis should be obtained, and where possible, the specific type of vasculitis should be identified. It is particularly important to recognise ANCA associated vasculitis in view of their poor prognosis and need for early treatment, but indiscriminate testing for ANCA in the absence of clinical evidence of vasculitis should be discouraged.

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